Get training let with Activity and 2 or more 161 Choose Next Descriptor Fit Non-Linear Parametric Expression to Descriptor Data more Descriptors? Select Descriptions For Selected Descriptors, allociates expressions to model done

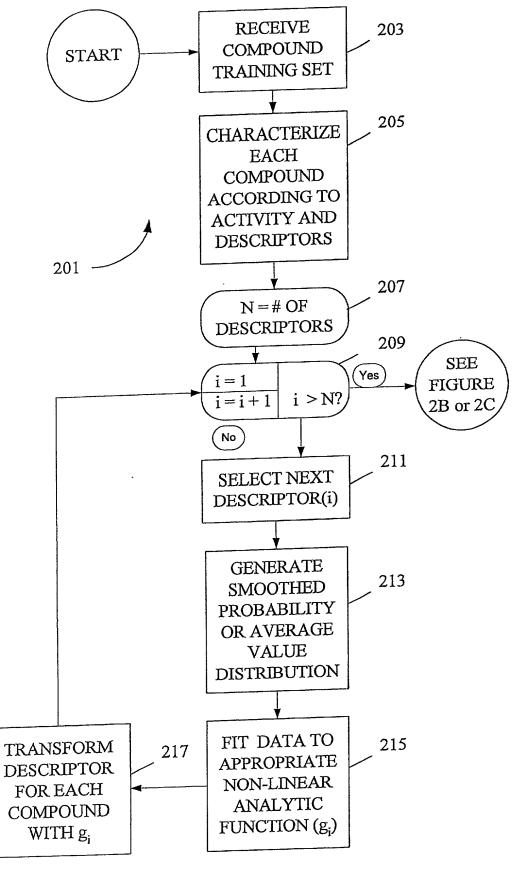
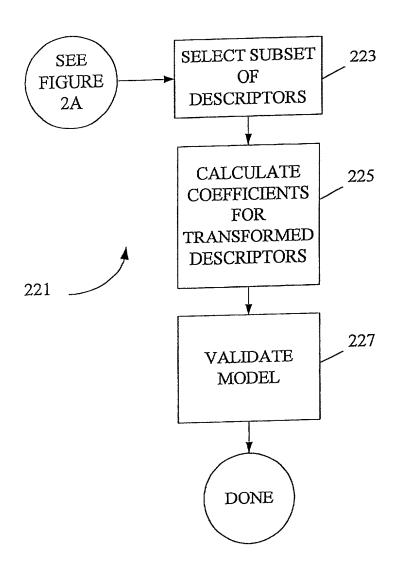


FIGURE 2A



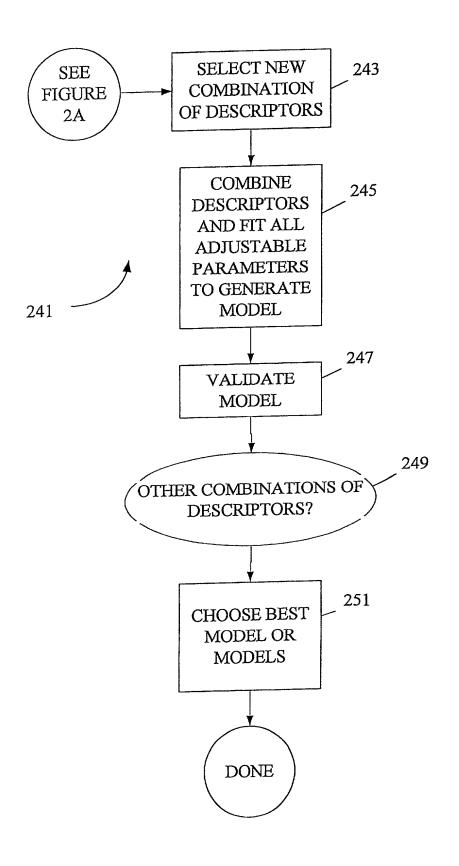
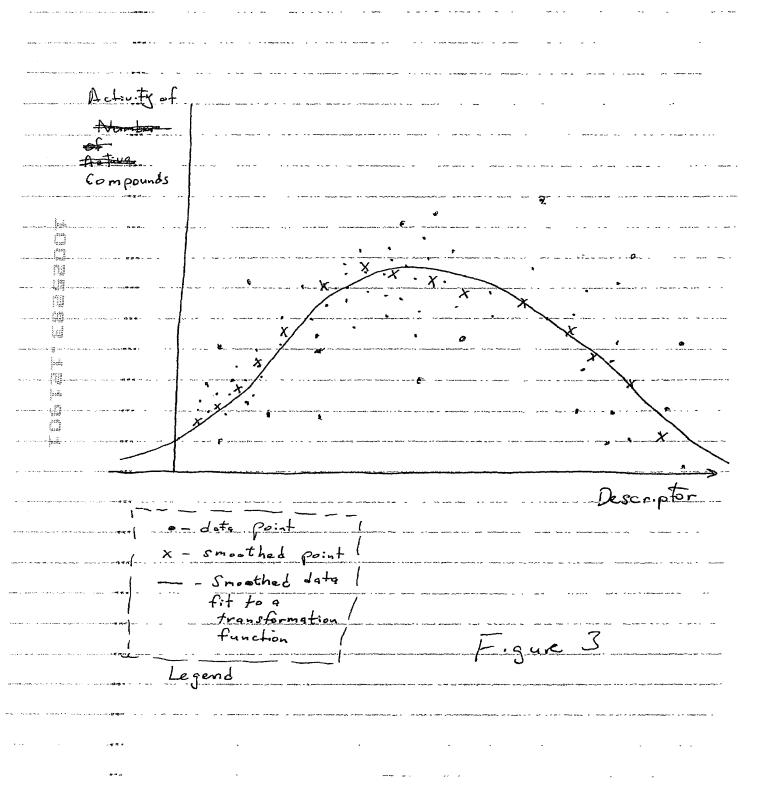
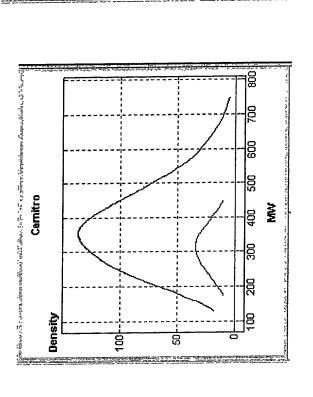
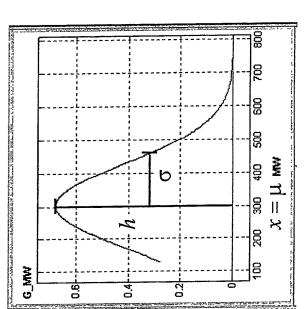


FIGURE 2C



Optimum Molecular Weight





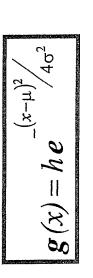


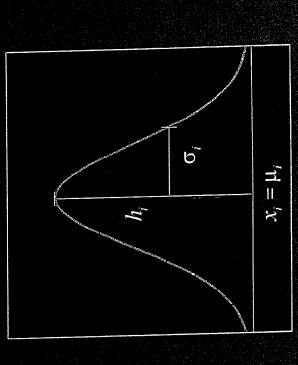
Figure 4A



N-Dimensional Gaussian Modeling

Additive

$$g(x_{i..N}) = \frac{1}{N} \sum_{i=1}^{N} h_i e^{-(x_i - \mu_i)^2 / 4\sigma_i^2}$$



Multiplicative

$$\mathbf{g}(x_{i..N}) = h e^{-\frac{1}{N} \sum_{i=1}^{N} (x_i - \mu_i)^2 / 4\sigma_i^2}$$

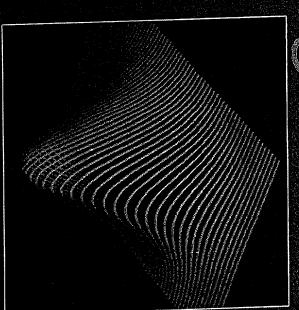


Figure 4 B

Optimization Function

$$g(\mathbf{x}, \boldsymbol{\mu}, \boldsymbol{\sigma}, h, t) = t + h e^{-\sum_{k=1}^{N_X} (x_k - \mu_k)^2 / 4\sigma_k^2}$$

$$f = s_{inh} \left[\frac{1}{N_{inh}} \sum_{i=1}^{N_{inh}} (\mathbf{g}(\mathbf{X}_i, \boldsymbol{\mu}, \boldsymbol{\sigma}, h, t) - \boldsymbol{y}_i)^2 \right]$$

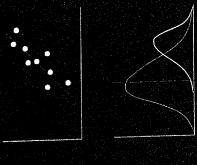
$$+ s_{drug} \left[\frac{1}{N_{drug}} \sum_{j=1}^{N_{drug}} \boldsymbol{g}(\mathbf{X}_j, \boldsymbol{\mu}, \boldsymbol{\sigma}, h, t) - \overline{y}_{drug} \right]^2$$

$$+ S_{fit} \left[\sigma_y^2 \sum_{k=1}^{N_x} \left(\frac{\mu_k - \mu_{0,k}}{range(X_k^T)} \right)^2 + (t - t_0)^2 \right]$$

Mean of the Squared Errors of Inhibitor Affinity

Squared Error of the Means of Drug Affinity

Constraints to prevent Overfitting





Initial Values for Optimization

$$t_{0} = min(y)$$
 $h_{0} = max(y) - t_{0}$

$$\sum_{i=1}^{N_{mh}} (y_{i} - t_{0})^{2} x_{k,i}$$

$$\sum_{i=1}^{N_{mh}} (y_{i} - t_{0})^{2}$$

$$= \frac{\sum_{i=1}^{N_{mil}} (y_i - t_0)^2 (x_{k,i} - \mu_k)^2}{\sum_{i=1}^{N_{mil}} (y_i - t_0)^2}$$

$$\sigma_{y} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_{i} - \overline{y}_{inh})^{2}}{N_{inh} - 1}}$$



Gaussian Optimization Function

$$f(x) = t + he^{-\sum_{k=1}^{N_x} (x_k - c_k)^2 / 4w_k^2}$$

$$= S_{\nu} \left(\frac{\sum_{i=1}^{N_{\nu}} u_i (f(\mathbf{x}_i) - y_i)^2}{\sigma_{\nu}^2 \sum_{i=1}^{N_{\nu}} u_i} \right)$$

$$+ S_c \sum_{k=1}^{N_v} \frac{\left(c_k - c_{0,k}\right)^2}{\sigma_{x_k}^2}$$

$$- S_W \sum_{k=1}^{N_X} \frac{\sigma_{X_k}}{W_k}$$

$$- s_t \frac{(t-t_0)^2}{\sigma_y^2}$$

Weighted Mean Squared Error



Width (Focus) Constraint

Tare Constraint

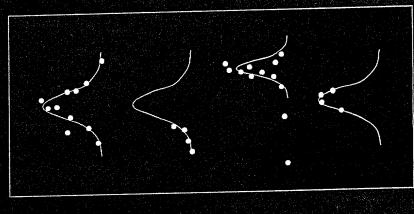


Figure 4E

Gaussian Optimization Starting Values

$$\sigma_{y}^{2} = \frac{\sum_{i=1}^{N_{inth}} u_{i} (y_{i} - \bar{y})^{2}}{\sum_{i=1}^{N_{inth}} u_{i}}$$

$$\sigma_{x_{k}}^{2} = \frac{\sum_{i=1}^{N_{inth}} u_{i} (x_{k,i} - \bar{x}_{k})^{2}}{\sum_{i=1}^{N_{inth}} u_{i}}$$

$$t_0 = min(y)$$

$$h_0 = max(y) - t_0$$

$$v_i = \frac{(y_i - t_0)^2}{\sigma_v^2}$$

$$C_{0,k} = \frac{\sum_{i=1}^{N_{inth}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{inth}} u_i v_i}$$

$$\sum_{i=1}^{N_{inth}} u_i v_i (x_{k,i} - c_{0,k})^2$$

$$\sum_{i=1}^{N_{inth}} u_i v_i (x_{k,i} - c_{0,k})^2$$

$$\sum_{i=1}^{N_{inth}} u_i v_i$$



Figure 4 F

Performance Metrics

$$n_k = \frac{\sigma_{x_k}}{w_k}$$

$$\sum_{i=l}^{N_v} u_i (f(\mathbf{x}_i) - y_i)^2$$

$$\bigvee_{i=1}^{N_{i,i}} u_{i}$$

$$= \frac{\left(\sum_{i=1}^{N_{v}} u_{i}(f(\mathbf{x}_{i}) - \bar{f}(\mathbf{x}))(y_{i} - \bar{y})\right)^{2}}{\sum_{i=1}^{N_{v}} u_{i}(f(\mathbf{x}_{i}) - \bar{f}(\mathbf{x}))^{2} \sum_{i=1}^{N_{v}} u_{i}(y_{i} - \bar{y})^{2}}$$

$$\int_{|z|} a_1(J(A_1) - J(A))$$

$$q^2 = I - S^2 / G_Y^2$$

Descriptor Focus

Standard Error

Correlation Coefficient

Residual Error



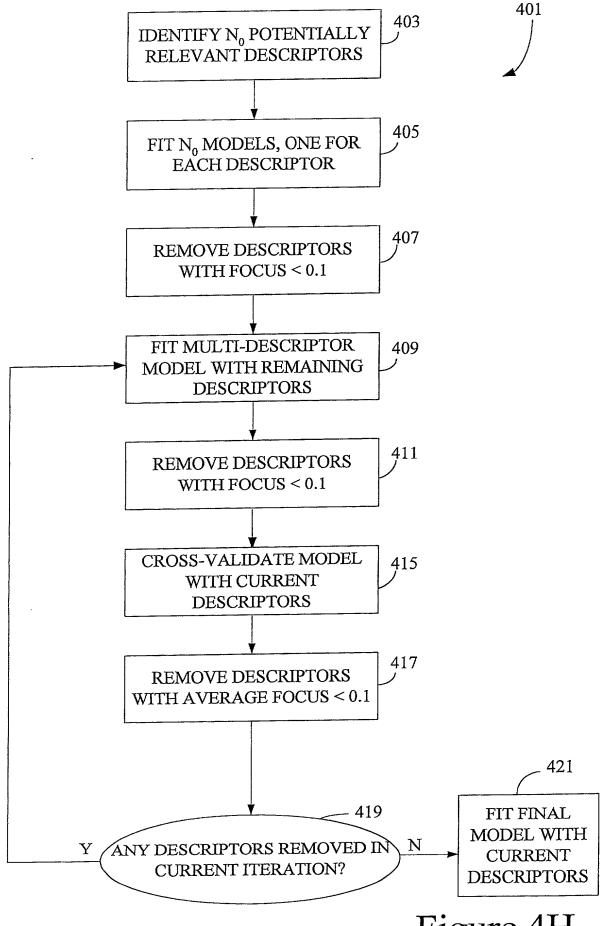


Figure 4H

Sigmoid Optimization Function

$$f(x) = t + \frac{h}{1 + \sum_{k=1}^{N_x} e^{-n_k (x_k - c_k)}}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_y} u_i (f(x_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right)$$

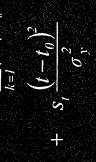
Weighted Mean Squared Error

$$+ S_c \sum_{k=l}^{N_{\chi}} \frac{\left(c_k - c_{0,k}\right)^2}{\sigma_{x_k}^2}$$

Center Constraint

$$- \sum_{k=1}^{N_x} |n_k| \sigma_{x_k}$$

Focus Constraint



Tare Constraint



Figure 4I

Sigmoid Optimization Starting Values

$$t_0 = min(y)$$

$$h_0 = max(\mathbf{y}) - t_0$$

$$v_i = \frac{\left(y_i - t_0\right)^2}{\sigma_y^2}$$
$$v_i' = \frac{\left(h_0 + t_0 - y_i\right)^2}{\sigma_y^2}$$

$$\sum_{h,k} = \frac{\sum_{i=1}^{m_i} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{mh}} u_i v_i}$$

$$C_{h,k} = \frac{\sum_{i=1}^{N_{mh}} u_i v_i^* x_{k,i}}{\sum_{i=1}^{N_{mh}} u_i v_i^*}$$

$$C_{l,k} = \frac{\sum_{i=1}^{N_{mh}} u_i v_i^*}{\sum_{i=1}^{N_{mh}} u_i v_i^*}$$

$$W_{h,k} = \sqrt{\frac{\sum_{i=1}^{N_{mh}} u_i v_i (x_{k,i} - c_{h,k})^2}{\sum_{i=1}^{N_{mh}} u_i v_i}}$$

$$w_{l,k} = \sqrt{\frac{\sum_{i=1}^{N_{mh}} u_i v_i' (x_{k,i} - c_{l,k})^2}{\sum_{i=1}^{N_{mh}} u_i v_i'}}$$

$$n_{0,k} = \frac{C_{h,k} - C_{l,k}}{W_{h,k} W_{l,k}}$$

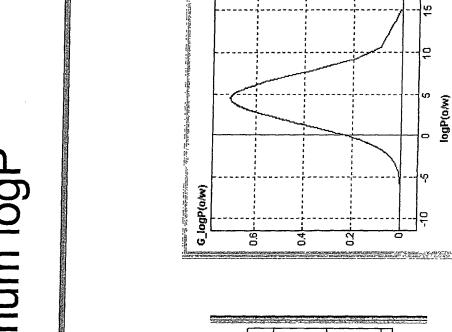
Figure 47

Start 501 descriptors for next compound Predict Binding 505 site Binding Does-Prediction More 507 Indicate Binding? 509 Obtain Property 511 Values Relevant to Electronic Reactivity Select Next Site on Compound Assess Reactivity of Sites? more From Roactvity Individual Sites Assess metabolic Reactify of prolecule

Figure 5

Receive Value of 603 505 Next Descriptor Descriptor Using ,605 Transformation Function Apply Transformed Descriptor to -607 Model Any More Descriptors in Model? Receive Value of Activity as a function of transformed Descriptors done

Optimum logP



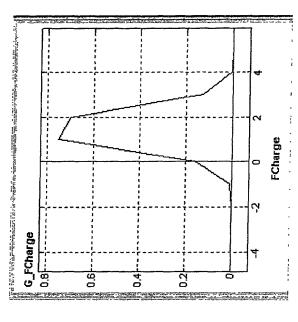
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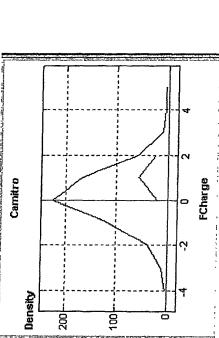
Density

Figure 7A

logP(a/w)

Optimum Formal Charge







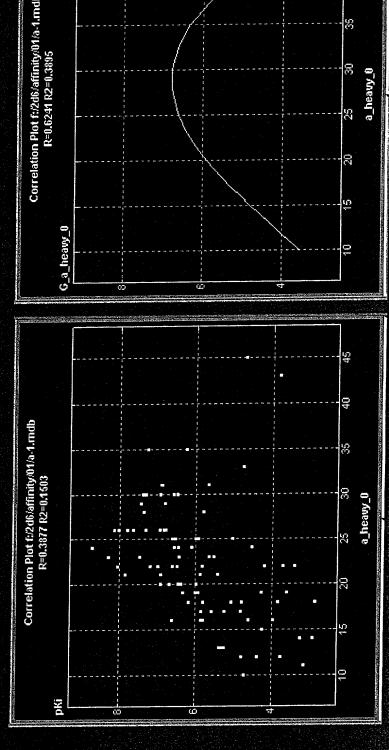
Automated Gaussian Fit

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Figure 7C

2D6 K_i Model

Non-linear Size Relation



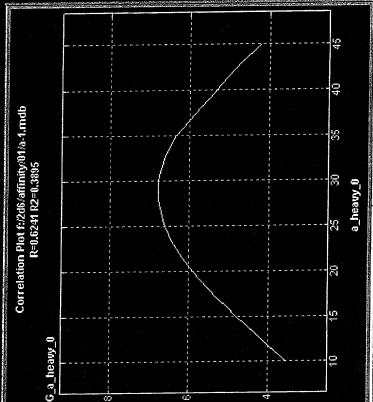


Figure 7D

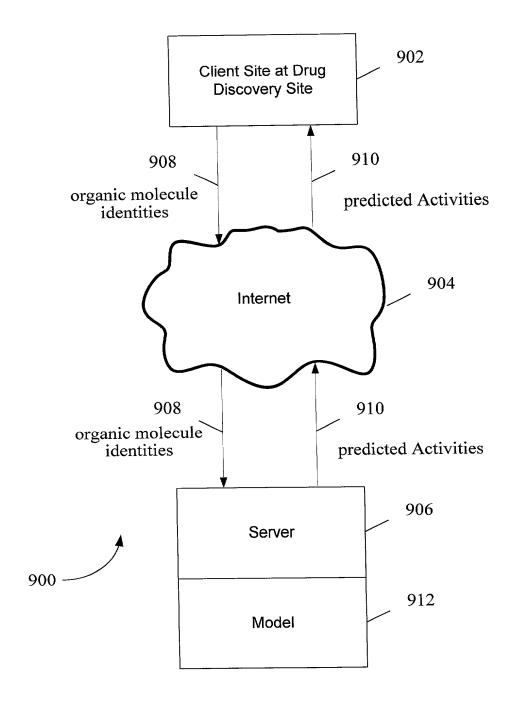


FIGURE 9

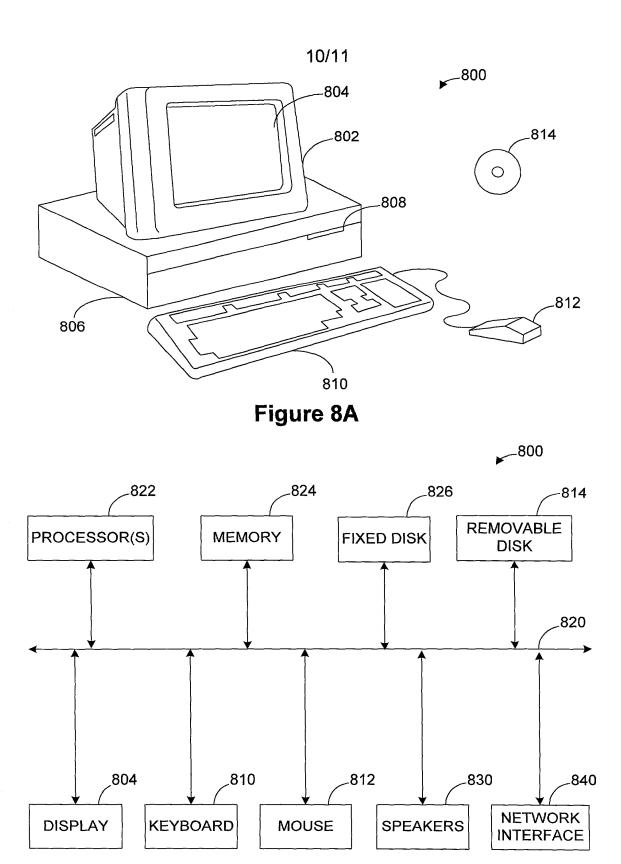


Figure 8B